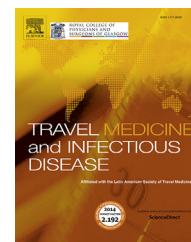


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REVIEW

Systematic review of loperamide: No proof of antibiotics being superior to loperamide in treatment of mild/moderate travellers' diarrhoea



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Summary Looking at the worldwide emergency of antimicrobial resistance, international travellers appear to have a central role in spreading the bacteria across the globe. Travellers' diarrhoea (TD) is the most common disease encountered by visitors to the (sub)tropics. Both TD and its treatment with antibiotics have proved significant independent risk factors of colonization by resistant intestinal bacteria while travelling. Travellers should therefore be given preventive advice regarding TD and cautioned about taking antibiotics: mild or moderate TD does not require antibiotics. Logical alternatives are medications with effects on gastrointestinal function, such as loperamide. The present review explores literature on loperamide in treating TD. Adhering to manufacturer's dosage recommendations, loperamide offers a safe and effective alternative for relieving mild and moderate symptoms. Moreover, loperamide taken singly does not predispose to contracting MDR bacteria. Most importantly, we found no proof that would show antibiotics to be significantly more effective than loperamide in treating mild/moderate TD.

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1. Introduction

Travellers' diarrhoea (TD) remains the most common medical problem encountered by travellers. WHO defines TD as three or more loose or liquid stools per day, or more frequently than is normal for the individual [1]. Although rarely severe and almost always spontaneously resolving [2–5], TD incurs significant morbidity and causes inconvenience to a high number of individuals: of all travellers to the (sub)tropics [6], 40–60% are expected to contract TD [2–4,7]. The inconvenience may not remain short-term: recent studies suggest that 3.0–13.6% of travellers with TD develop post-infectious irritable bowel syndrome (IBS) [8–13].

Antimicrobials have for decades been considered the primary option in treatment [14] – and even prevention [15–17] – of TD. One justification for this approach has been its presumed potential to prevent postinfectious IBS. However, we did not find any investigations that would have shown antibiotic treatment of TD to prevent IBS. On the contrary, one study suggests that taking antimicrobials actually increases the risk of post-travel IBS [9]. The increase of antimicrobial resistance raises serious concern over excessive antibiotic use [18–20]. The use of antibiotics for TD adds to this problem, as the drugs predispose travellers to contracting multidrug-resistant (MDR) bacteria which they may eventually spread to their home countries [21–23]. Besides global health care, antibiotics may harm individuals, not only by increasing the risk of infections by MDR bacteria, but by causing long-lasting changes in the intestinal microbiota [24]. Therefore, many current guidelines do not encourage treating TD with antibiotics [25]. In recent research, however, fairly little attention has been paid to non-antibiotic drugs with effects on the gastrointestinal function. These include loperamide, diphenoxylate plus atropine, and rasecondrontil, drugs of which loperamide has been available for decades, whereas racecadotril, despite its indication for acute diarrhoea [26], has so far not been studied among travellers. In a recent study, loperamide taken singly did no predispose to contracting MDR bacteria [27].

In this review we discuss the effectiveness and safety of loperamide in treating TD.

1.1. Loperamide – pharmacological aspects

Loperamide is an oral opioid-like agent which is considered nonabsorbable: only insignificant amounts reach the systemic circulation and even less penetrate the blood-brain barrier [28]. Therefore, at recommended dosages, the drug lacks central opioid-like effects, including centrally mediated blockade of intestinal propulsion [29]. In the intestine, it has an antisecretory effect mediated via μ -opioid receptors and non-opioid-receptor mechanisms. At higher dosages, however, loperamide also decreases motility, an effect mediated via μ -opioid receptors in the myenteric plexa of the bowel. Both of these mechanisms may be covered by dosage recommendations: low doses exploit the antisecretory and higher ones the antimotility effect [30]. Loperamide undergoes first-pass metabolism by CYP3A4 and CYP2C8 [31], a point of potential relevance when

concomitantly using medicines metabolized through the same enzyme systems.

Loperamide is currently marketed in 110 countries. The recommended regimen is a 4-mg loading dose followed by 2 mg after every episode of diarrhoea. Some manufactures recommend that in acute disease the maximum dose would be 12 mg/day and the drug should not be used for longer than 48 h [32], while others allow 16 mg and even five-day-use [33].

1.2. Effects of various pathogens on bowel functions

The total fluid turnover of the intestine is about eight litres per day, most of which will be re-absorbed. The various intestinal pathogens may disturb the normal intestinal functions in differing ways as described below.

Many intestinal pathogens, with enterotoxinogenic *Escherichia coli* (ETEC) and *Vibrio cholerae* as two well-known examples, produce enterotoxins which stimulate the active water transport mechanisms of the enterocytes via ATP-dependant sodium/potassium pumps (secretory diarrhoea) [34]. As obvious, the antisecretory effect of loperamide is especially advantageous in this setting.

The main pathogenetic mechanism of some other pathogens, such as *Campylobacter* spp. and *Salmonella* spp., is not enterotoxin-mediated but, instead, the invasive nature of the bacteria determines the clinical picture: the bacteria invading the mucous membrane cause inflammation and ulcerations [35]. Blood and plasma leaking into the lumen draw even more fluid from the systemic circulation through osmosis. In addition, the widespread apoptosis of enterocytes leads to a decrease in the total resorptive ability of the bowel. Loperamide appears to have some effect even in this setting [36], probably by diminishing fluid secretion from the remaining viable enterocytes. Loperamide has been suggested to be harmful in infections with invasive pathogens: through its antimotility effect it may prevent the natural mechanism where pathogens are washed out. Accordingly, the drug is not recommended for cases with high fever or overtly bloody diarrhoea [14,25,32,33].

In cases with *Clostridium difficile* as a potential pathogen, loperamide and all other agents decreasing intestinal motility should be avoided, at least initially. If the diagnosis is confirmed, administering loperamide in conjunction with antibiotics effective against *C. difficile* is probably safe [37], although many experts advise against it [38–42]. Most importantly: when *C. difficile* is suspected, loperamide should not be used without an effective anti-clostridial agent [37].

2. Methods

2.1. Loperamide and travel – systematic search for studies

PubMed search with terms “loperamide” and “travel” yielded 86 articles, 71 of which were in English. From them we excluded five letters and 34 reviews on a subject other than loperamide; one case report did not focus on

loperamide, and in two it was not administered to travellers. Finally, a total of 29 articles were included in this review (Fig. 1, Tables 1–3).

2.2. Search for case reports on serious adverse events

Since no serious adverse events were reported in the articles we found applying the criteria above, we ran a further search in PubMed using the terms loperamide and “adverse”, “death”, “fatal”, “megacolon”, “ileus”, “necrotising colitis”, OR “perforation”. This search was not restricted to travellers. In addition, we reviewed the authors’ archives. Finally, 24 case reports altogether were included (Table 4).

3. Results

3.1. Effectiveness of loperamide in travellers’ diarrhoea: randomized trials

Of the 15 randomized trials conducted among travellers, four were carried out with US military personnel, one with both military and tourists, and the remaining 11 with students or ordinary tourists. There were nine investigations with Mexico as the destination which included 59% of all

research subjects. The results of these studies are summarized in Table 1.

In 2008, Riddle et al. [43] published a review and meta-analysis of loperamide as an adjunct to antibiotic treatment for TD. The combination was found more effective than antibiotics alone in five studies [44,45,48,51,52]; one of them reported, however, that the effect had seemed to wane by the fourth day [52]. In one study, adding loperamide had not shortened the illness despite reducing bowel movements [47]. In the meta-analysis, the difference between the combination and antibiotics alone groups proved no longer significant after the second day of treatment: the authors attributed this to the benign course of the disease, speculating that those with ongoing symptoms even on the third day had probably been infected with an invasive pathogen. It is also noteworthy that loperamide had been taken for two days only. The authors concluded that loperamide can be used even in invasive disease, yet further studies would be needed. The use of loperamide as single treatment for less severe disease was also discussed, and adding antibiotics was recommended against symptoms that do not resolve within 12 h.

We only found two RCTs [44,52] comparing antibiotics to loperamide taken alone in treating TD. Ericsson et al. [44] reported loperamide to be equal to cotrimoxazole. DuPont et al. [52] found rifaximin to be more effective than loperamide in reducing the TLUS (time from administration

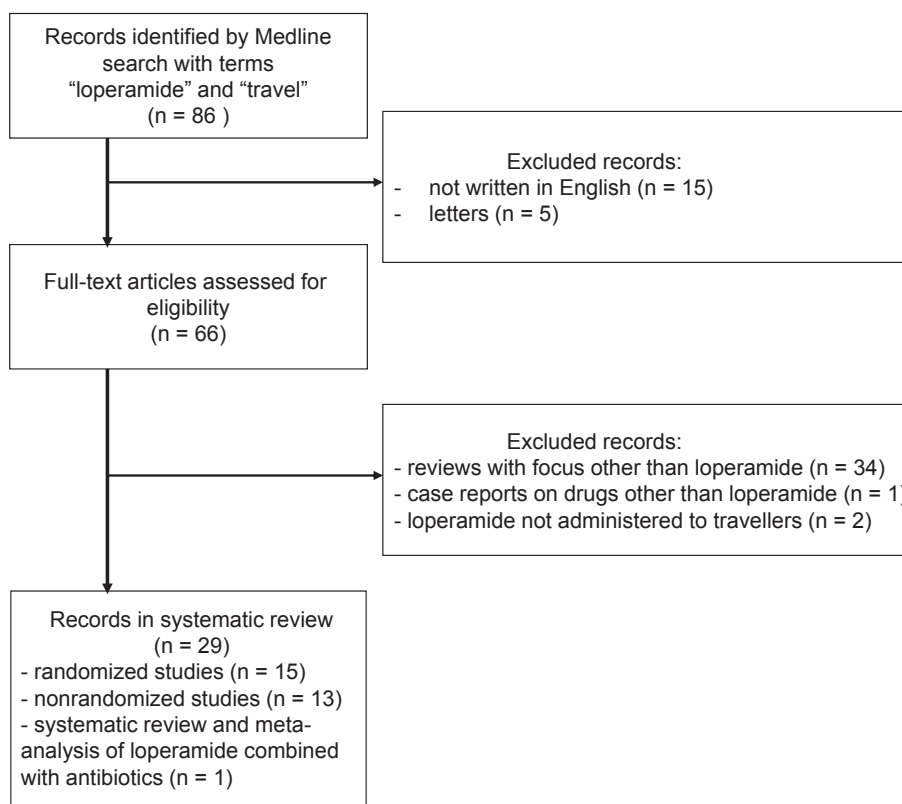


Figure 1 Flow diagram illustrating the article search of our systematic review. In addition, case reports on serious adverse effects of loperamide were collected in authors’ archives and in the PubMed with the terms: “loperamide” and “adverse effect”, “death”, “fatal”, “megacolon”, “ileus”, “necrotising colitis”, OR “perforation”. The search for cases was not restricted to travellers; a total of 24 reports were included.

Table 1 The results of a systematic review on loperamide for TD among travelers: randomized studies.

First author, year	Destination of travel	Type of study	Population	Patients in entire study	Study subjects with TD	Serious adverse events	Loperamide max dose	Medications used/compared	Safety: LO against recommendations	Effectiveness
Randomized trials										
Studies included in Riddle et al meta-analysis										
Riddle (meta-analysis 2008) [43]	Various destinations	Meta-analysis of randomized controlled trials	Travellers and US military	1435	1435	No SAE*	16 mg		-Proportion of invasive pathogens: 11% <i>Shigella</i> , 11% <i>Campylobacter</i> 4% <i>Salmonella</i>	AB + LO > AB
Ericsson 1990 [44]	Mexico	RCT	Student travellers	227	227	No SAE*	16 mg	LO 41% TMP-SMX vs LO alone vs combination	9/93 bloody stools 2 cases with <i>Campylobacter</i>	AB + LO > LO = AB
Taylor 1991 [45]	Egypt	RCT	US military personnel	104	104	No SAE	16 mg	LO: 48% (CIP+/- LO)	Exclusion criteria: Bloody stools or high fever	AB + LO = AB
Ericsson 1992 [46]	Mexico	RCT	Student travellers	190	190	No SAE	16 mg	LO: 100% TMP-SMX (dosing)+LO	Exclusion criteria: Bloody stools or high fever 10 cases with <i>Shigella</i>	All used LO
Petrucelli 1992 [47]	Thailand	RCT	US military personnel	142	142	NR	16 mg	LO: 65% (CIP +/- LO)	Exclusion criteria: Bloody stools, high fever or TD > 4 days 37% microscopic blood in stools 41% <i>Campylobacter</i> 18% <i>Salmonella</i> 4% <i>Shigella</i>	No differences in duration of illness (but fewer bowel movements)
Ericsson 1997 [48]	Mexico	RCT	Student travellers	166	166	No SAE	16 mg	LO: 33% OFL +/-LO	12/54 fever in LO-group 5 <i>Shigella</i> in LO group.	AB + LO > AB
Ericsson 2001 [49]	Mexico	RCT	Student travellers	88	88	No SAE	16 mg	OFL + LO 100%	Bloody stools or high fever exclusion criteria 10% developed fever	All used LO
Sanders, 2007 [50]	Turkey	RCT	US military personnel	207	207	No SAE	16 mg	LO 100% Azithro + LO vs levo + LO	Exclusion criteria: Bloody stools or high fever 7% <i>Campylobacter</i>	All used LO
Ericsson, 2007 [51]	Mexico	RCT	Student travellers	176	276	No SAE*	16 mg	LO: 34% (Azithro+/-LO)	11/59 (59 used LO) bloody stools, no fever	AB + LO > AB
DuPont, 2007 [52]	Mexico	RCT	Student travellers	310	310	No SAE,*	Max. 8 mg/day for 2 days	LO 34% RIF + LO 34% RIF 33%	Exclusion criterion: Bloody stools Fever not reported 4 cases with <i>Shigella</i> in LO groups	Day1: AB + LO > AB = LO Day4: AB + LO = AB > LO

Studies not included in Riddle's meta-analysis

Johnson 1986 [53]	Latin America	Randomised nonblinded trial	Travellers	219	219	No SAE*	16 mg	LO 51% Bismuth salicylate 49%	Exclusion criteria: Bloody stools or high fever 12 of the users of lo had <i>shigella</i>	LO > bismuth salicylate
duPont 1990 [54]	Mexico	RCT	Student travellers	203-> 180 eligible for analyses	180	No SAE*	8 mg	LO 45% Bismuth salicylate 55% (LO vs bismuth)	Exclusion criteria: Bloody stools, high fever or TD requiring AB	LO > Bismuth salicylate
Okhuysen 1995 [55]	Mexico	RCT	Student travellers	173	173	No SAE*	16 mg	LO 34% Zaldaride 33% Placebo 33%	Exclusion criteria: Bloody stools or high fever <i>Shigella</i> 9%, <i>salmonella</i> 2%	LO > Zaldaride = placebo
Silberschmidt 1995 [56]	Egypt	RCT	Travellers	436 TD; 331 original analysis	331	No SAE*	16 mg	LO 27% Zaldaride 56% Placebo 17%	Exclusion criteria: Bloody stools <i>Salmonella</i> 2%, <i>Shigella</i> 1%	Zaldaride = LO > placebo
Caeiro 1999 [57]	Mexico	Randomised nonblinded trial	Travellers	80	80	No SAE*	8 mg	LO 100% ORT 50%	Not reported	ORT did not add efficacy
Letizia, 2014 [58]	Turkey	Randomised nonblinded trial	US military personnel	109	109	No SAE*	NR	LO 69% AB 19%	Not reported.	Pre-deployment provision of LO did not diminish the use of AB. AB use 15/62

RCT = randomized controlled trial.

LO = loperamide.

CIP = ciprofloxacin.

RIF = rifaximin.

OFL = ofloxacin.

TMP-SMX = cotrimoxazole.

TD = travellers' diarrhoea.

AB = antibiotic.

SAE = serious adverse event.

Table 2 The results of a systematic review on loperamide for TD among travellers: nonrandomized studies.

First author, year	Destination of travel	Type of study	Population	Patients in entire study	Study subjects with TD	Serious adverse events	Loperamide max dose	Medications used/compared	Safety: LO against recommendations	Effectiveness
Prospective studies										
Hill 2000 [59]	Various destinations	Prospective questionnaire	Travellers	784; 270 had TD and 88 "loose motions"	358	NR	NR	antimotility agent (mainly LO) or bismuth salicylate alone: 43% AB: alone 11% antimotility/ bismuth + AB 22%	22% fever 1.5% blood in stools	No difference in subjective effectiveness between antimotility/ bismuth, AB or combination
Peetermans 2001 [60]	Various destinations	Prospective questionnaire	Travellers	84; 43 (51%) TD	43	NR	NR	LO 79% AB 5%	3/43 bloody stools 3/43 high fever	Not reported
Pitzurra 2010 [3]	Various destinations	Prospective questionnaire	Travellers	2800; all diarrhoea	1265	NR	NR	AB 58% AB 5%	166 bloody stools; of these AB: 21%, LO alone: 23%	Not reported
Porter 2010 [61]	Turkey	Prospective questionnaire	US military	202	202	NR	NR	LO 87% AB 100%	8% bloody stools, 34% fever	Not reported
Soonawala 2011 [2]	Various destinations	Prospective questionnaire	Travellers	390; 160 TD	160	NR	NR	LO 33% AB 9%	Not reported	Not reported
Belderok 2011 [4]	Various destinations	Prospective questionnaire	Travellers	1202/781 subjects with TD	781	NR	NR	AB 5% antimotility such as loperamide 30% AB 30% LO not reported	14% fever 4% bloody stools	Not reported
Lalani 2015 [12]	Various destinations	Prospective questionnaire	US military personnel	1120; 270 had TD (24%)	270	NR	NR	LO alone 31% LO + AB: 5%	23% had febrile diarrhoea or bloody stools	AB did not shorten the course of disease
Kantele 2016 [27]	Various destinations	Prospective questionnaire	Travellers	288	288	No SAE (unpublished data)	NR		Unpublished data: 15% of LO users had fever >37.5	Not reported
Retrospective studies										
Meuris 1995 [62]	North Africa	Retrospective questionnaire	Travellers	adults 5373 (2000 = 37.2 TD) children 818 (225 = 27.5% TD)	2225 (225 children!)	NR	No SAE*	43% LO 11% AB + LO	22% took LO for severe TD +29% LO + AB	LO > AB = no treatment, but AB treatment was nifuroxazide
Reinthal 2004 [63]	Various destinations	Retrospective questionnaire	Travellers	434 with TD	434	NR	NR	LO 40% AB 29%	Not reported	Not reported
Sanders 2005 [64]	Egypt	Retrospective questionnaire	Us military	129 with TD	129	NR	NR	LO 13% LO + AB 83%	25% fever 2% bloody stools –7 <i>Campylobacter</i> , 2 <i>Shigella</i>	96% used LO

Putnam 2006 [65]	Iraq, Afghanistan	Retrospective questionnaire	US military personnel	15459 8096/10833 75% had TD	8096	NR	NR	LO 37% AB 27% + self-treatment with LO 15% and with AB 8% LO 34% LO + AB 13%	26% fever, 8% bloody stools	Not analysed
Brown et al., 2009 [66]	Iraq and Afghanistan	Retrospective questionnaire	US military personnel	1259 (diarrhoea treatment) 2674 (treatment satisfaction)	1259	NR	NR		Not reported	Post-treatment duration of diarrhoea: AB = LO LO > ORT LO + AB = ORT LO = LO + AB AB = AB + LO

LO = loperamide.
 CIP = ciprofloxacin.
 RIF = rifaximin.
 OFL = ofloxacin.
 TMP-SMX = cotrimoxazole.
 TD = travellers' diarrhoea.
 AB = antibiotic.
 SAE = serious adverse event.

of first dose until passage of last unformed stool), yet the mean number of unformed stools was lower in the loperamide group the first day of treatment. On day five, no significant differences remained. It should be noted that the subjects in the loperamide group only took the medicine for two days, while those in the rifaximin group continued treatment for three.

Loperamide proved more effective than bismuth salicylate in one RCT [54] and in one randomized nonblinded trial [53]. In other studies, loperamide was found more effective than zalaride maleate and placebo [55], or equal to zalaride maleate, but more effective than placebo [56].

In another investigation, oral rehydration therapy did not prove to add effectiveness to loperamide taken singly [57]. Furthermore, in a study exploring pre-deployment provision of loperamide the need for antibiotics was not decreased [58].

In the majority of randomized studies, patients with high fever and bloody stools had been excluded before randomization. However, invasive pathogens were detected in many cases. No serious adverse events were reported (Table 3).

3.2. Effectiveness of loperamide in travellers' diarrhoea: nonrandomized studies

The nonrandomized studies comprised seven prospective and five retrospective questionnaire-based studies (Table 2); the number of subjects with TD varied between 43 and 8096. In none of the observational studies reporting outcomes were antibiotics found superior to loperamide taken singly [12,59,62,66]. The duration of post-treatment diarrhoea was similar among 1259 US military personnel regardless of whether they had used loperamide or antibiotics alone or together as combination therapy [66]. Hill et al. [59] found no differences in subjective effectiveness between antimotility agent (mostly loperamide) and bismuth salicylate, and antibiotics and their combination among 358 travellers with TD or "loose motions", not even in the moderate/severe groups. Loperamide taken singly was proved superior to nifuroxazide in an investigation carried out by Meuris et al. [62] with travellers to North Africa.

3.3. Serious adverse events in randomized/nonrandomized studies reporting use of loperamide for TD

None of the questionnaire-based studies reported serious adverse events (either did not report adverse events at all or they were not severe) (Table 3). Some of these investigations included a substantial proportion of travellers with severe TD and even dysentery, but only a few studies where loperamide was taken singly presented data on the proportion of those with severe TD/dysentery: Pitzurra et al. [3] explored 1265 volunteers with TD, and found that out of the 166 travellers with dysentery, 38 (23%) had used nothing but loperamide. Likewise, in an earlier investigation [62], 22% of the subjects had only taken loperamide for severe TD, yet no serious adverse events were reported.

Table 3 Studies that report any adverse effects.

First author, year	Adverse effects in LO group	Adverse effects in placebo group	Adverse effects in groups with other treatments
Johnson 1986 [53]	8 cases with constipation (7.2%)	No placebo group	Bismuth subsalicylate: 1 case with constipation (0.9%)
duPont 1990 [54]	Unspecified minimal adverse effects (proportion not reported)	No placebo arm	Bismuth subsalicylate: unspecified minimal adverse effects (proportion not reported)
Ericsson 1990 [44]	NR	NR	1 case of rash with TMP-SMX
Okhuysen 1995 [55]	31% unspecified adverse effect	17% unspecified adverse effect	Zaldaride maleate: Unspecified adverse effect 22%
Silberschmidt 1995 [56]	13% unspecified adverse effect	15% unspecified adverse effect	11–15% unspecified adverse effect with zaldaride maleate
Meuris 1995 [63]	Constipation 2.4%	No placebo group	Those who took nifuroxazide took also LO
Caeiro 1999 [57]	10% unspecified minor adverse effects	No placebo group	15% unspecified minor adverse effects
DuPont, 2007 [52]	Any adverse effect: 74%, Constipation: 7% Nausea 22% Vomiting: 12% (significant difference vs. RIF alone) Abdominal cramps 33% (significant difference vs. LO + RIF)	(RIF alone) Any adverse event: 69% Constipation: 5% Nausea: 11% Vomiting: 3% Abdominal cramps 23%	(RIF + LO) Any adverse event: 64% Constipation: 8% Nausea: 18% Vomiting 4% Abdominal cramps: 13%
Ericsson, 2007 [51]	1/56 rash, 4/56 headache	No placebo group	All received azithromycin; Azithromycin alone: 1/106 rash, 7/106 headache, 1/106 dizziness
Letizia, 2014 [58]	1 case with constipation (2.1%)	No placebo group	6 cases with constipation in the nonloperamide group (9.8%)

LO = loperamide.

RIF = rifaximin.

TMP-SMX = cotrimoxazole.

TD = travellers' diarrhoea.

AB = antibiotic.

SAE = serious adverse event.

To sum up, in all of the randomized or nonrandomized studies found applying the search criteria set for this review (Tables 1–3), only mild adverse effects were detected. This prompted us to run yet another search in PubMed on possible case reports (see below) and include, besides TD, also other indications for taking the drug.

3.4. Case reports on serious adverse events with loperamide

Searching further, twenty-four case reports (Table 4) were discovered to include a suspicion of serious, in some cases fatal, complications in patients having used loperamide.

There were seven cases with severe cardiac arrhythmias [86–88] and two cases leading to death [77,85] where the patients had taken an overdose of loperamide ranging from 70 mg to almost 800 mg. Two cases with anaphylaxis were reported [76,78], one of them fatal. In another fatal case loperamide had been administered to a patient taking clozapine during an outbreak of diarrhoea, and the additive anticholinergic effect was speculated to have contributed

to toxic megacolon [74]. Two cases with necrotising enterocolitis [69] and two with paralytic ileus [68] concerned infants treated with loperamide; one was a clear misuse (1.4 mg/kg administered to a 17-month-old baby).

In two case reports with toxic megacolon, loperamide had been used for diarrhoea when treating patients previously given broad-spectrum antibiotics [70,79]; *C. difficile* was eventually identified as the causative pathogen.

Five case reports described acute pancreatitis [72,81,83,89,90]. One was recurrent: both episodes had been preceded by use of loperamide with normal dosage (6 mg). Two patients had taken an overdose of loperamide [72,81].

With the exception of the cases of anaphylaxis [76,78] and catatonia [84], there were seven which could be attributed to TD-like conditions. In two cases (toxic megacolon with *Campylobacter* and bacteraemia caused by *Shigella*), loperamide was used by a patient with bloody stools [73,82]. In addition, there were four cases with necrotising enterocolitis (three with perforation), in which loperamide had been taken for three days by three patients

Table 4 Case reports on serious adverse events with users of loperamide.

First author, year	Serious adverse event diagnosis	Serious adverse event description
Brown 1979 [67]	Toxic megacolon	Patient had ulcerative colitis, used LO for chronic diarrhoea. Dose/length of use not specified.
von Muhlendahl 1980 [68]	Paralytic ileus	2 infants were treated with LO; one-year-old with a single dose (0.045 mg/kg), and a 17-month-old with an overdose (1.4 mg/kg)
Chow 1986 [69]	necrotising enterocolitis	2 infants were treated with LO, paralytic ileus prior to necrotizing enterocolitis: 3-month-old had been treated with 0.4 mg/kg for two days and a 7-month old 0.4 mg/kg for two days
Walley 1990 [70]	Toxic megacolon	LO 6 mg/day for 2 weeks. <i>Clostridium difficile</i> was detected in the faeces only at the diagnosis of toxic megacolon.
Olm 1991 [71]	Two cases of necrotising enterocolitis with perforation	Both patients had been treated with LO 12 mg/day for 3 days
Epelde 1996 [72]	Acute pancreatitis	A case with LO overdose (24 mg)
Schneider 2000 [73]	Toxic megacolon	Toxic megacolon due to the use of loperamide (dose not given) and <i>Campylobacter</i> infection. The patient had bloody stools.
Eronen 2003 [74]	Death	LO (dose not reported) used in an epidemic of gastroenteritis (later confirmed as <i>Bacillus</i> spp). Toxic megacolon was interpreted to be due to anticholinergic effects of clozapine combined with LO.
Caumes 2004 [75]	Case 1: necrotizing colitis with perforation Case 2: necrotising colitis	case 1: LO (dose not reported) 3 days case2: LO 15 days
Perez-Calderon 2004 [76]	Anaphylaxis	2 mg tablet against acute gastroenteritis
Sklerov 2005 [77]	Death	Overdose of loperamide (dose not specified)
Srinivasa, 2007 [78]	Death due to anaphylaxis	Death due to anaphylaxis after ingestion of 2 × 2 tablets of LO
Kato 2007 [79]	Toxic megacolon	Patient had diarrhoea 3 weeks after administration of broad-spectrum antibiotics, eventually <i>C. difficile</i> was detected. LO dose not reported
McGregor 2007 [80]	Fulminant amoebic colitis	Patient had used LO against TD 8 mg/day for 14 days
Lee 2011 [81]	Acute pancreatitis	Elevation of pancreatic enzymes after overdose of loperamide (18 mg) and trimebutine (600 mg)
Grondin 2012 [82]	<i>Shigella flexneri</i> bacteremia	Patient had used LO (dose not reported) for bloody diarrhoea for five days
Vidarsdottir 2013 [83]	Acute pancreatitis	Used LO for 2 days: 10 mg on the first day, 6 mg on the second
Di Rosa 2014 [84]	Catatonia	12 mg of LO over 12 h (18 mg over 30 h). Catatonia resolved with naloxone.
Dierksen 2015 [85]	Death	LO abuse, serum levels six times peak therapeutic
Enakpene 2015 [86]	Long QT and syncope	Abuse of LO. Had probably taken several bottles of LO.
Mancano 2015 [87]	Cardiac arrhythmias	5 cases with cardiac arrhythmias after overdose/abuse of LO 35-398 tablets
Spinner 2015 [88]	Ventricular tachycardia	LO 144 mg daily for two years
Labgaa 2015 [89]	Recurrent acute pancreatitis	Used LO 6 mg/day for 2 days; the first episode was also preceded by the use of LO.

and for two weeks by one [71,75]. The patient with fulminant amoebic colitis had used loperamide for two weeks [80].

4. Discussion

Initially, loperamide was believed to have the same antimotility effect as diphenoxylate with atropin (Lomotil) and similar agents. There is still a widespread conception that the numerous adverse effects of these older antimotility agents (e.g. toxic megacolon, pancreatitis, paralytic ileus, anorexia, rash, itch) [91] also apply to loperamide. Later studies have shown, however, that loperamide should not be grouped together with these agents: in fact, given at lower dosages, loperamide has minimal effect on motility, while antimotility activity is only seen with larger doses [92].

The idea of using a drug like loperamide may be rejected by travellers who prefer not to suppress diarrhoea which they consider a part of our natural defence against intestinal pathogens. This view is challenged by the current perception that, rather than a host defence mechanism, secretory diarrhoea is triggered and exploited by the pathogen simply to facilitate transmission to new individuals [93]. This perception is nicely illustrated by cholera, a disease where diarrhoea volumes may reach 20 L per day, resulting in severe dehydration and even death of the host. The same reasoning applies to enteroinvasive infections: none of the steps in their pathogenesis appear beneficial to the host defence system. There is a secretory component even in this setting, but the most important pathogenic mechanism seems to consist in causing direct damage to the epithelium, leading to leakage and poor uptake of water [92].

Current data suggest that loperamide has a potent antisecretory effect even at low dosages [92], while higher doses (above 12 mg) decrease motility [30,92]; this entails a further increase in fluid absorption when the transit time is prolonged, applying both to secretory and enteroinvasive diarrhoea. However, at least in theory, higher dosage might also prove harmful, for it may indicate a simultaneous increase in exposure of the epithelium to microorganisms and toxins. Taken together, the current literature suggests that at moderate dosage, loperamide mostly has an antisecretory effect and bowel motility is not affected to the same extent; no data implicate that the drug would be unsafe.

4.1. Loperamide vs. antibiotics for TD

Interestingly, our literature search only yielded two randomized trials [44,52] comparing loperamide and antibiotics in TD, neither of them with fluoroquinolones or macrolides. In 1990, Ericsson et al. [44] found loperamide used singly equal to cotrimoxazole. In the study by DuPont et al. [52], loperamide was found inferior to rifaximin when measured as TLUS, yet the mean number of loose stools on day one was lower in the loperamide than the rifaximin group. On day five there was no significant difference in the "wellness achieved".

In addition to the RCTs, we found a few observational studies looking at the effectiveness of loperamide:

antibiotics were not shown to be more effective than loperamide in any of the observational studies either [12,59,62,66]. Despite lacking proof of the superiority of antibiotics, in some guidelines [14] they are recommended as the primary treatment options. If there is no difference in efficacy, adverse effects and other potentially harmful long-term consequences should be weighed up. The discussion below will cover data on potential serious adverse effects, focusing first on loperamide and then on antibiotics. It will also remark that during the last decade, the sensitivity of diarrhoeal bacteria to empiric antibiotics has been steadily decreasing.

4.2. Serious adverse effects of loperamide

Widely used by travellers against TD, loperamide has proved effective and safe in both randomized trials and observational studies (Tables 1–3), when taken according to recommendations. Despite high fever or dysentery being exclusion criteria for loperamide use in almost all randomized studies, cases with invasive pathogens had been found in most of them, if analysed. In nonrandomized studies, loperamide had also been used by patients with high fever or dysentery, yet only few reports specify the proportion of such patients: in the study by Pitzurra et al. [3], 21% used loperamide singly in dysentery.

Four case reports of severe cardiac arrhythmias concerned patients with massive overdoses of loperamide. At very high dosage, loperamide is able to cross the blood-brain barrier and activate central opioid receptors, leading to euphoria and analgesia, but also respiratory depression and other opioid side effects [85]. Because of this, abuse of loperamide is sometimes referred to as "poor man's methadone" [85,94].

In most of the case reports on serious adverse events with loperamide (Table 4), the drug had been used against recommendations: for diarrhoea resulting from use of broad-spectrum antibiotics [70,79], for bloody diarrhoea [72,82], to treat infants [68,69] or with intake lasting weeks instead of days [70,75,80]. However, six of the case reports comprised patients who had used loperamide according to manufacturers' recommendations [71,74,76,78,83,89], or whose deviation from the guidelines was minimal [86].

4.3. Harmful effects of antibiotics

Although not common, the most frequently used TD antibiotics, fluoroquinolones and macrolides, are known to potentially cause severe adverse effects, such as anaphylaxis [95,96], Stevens-Johnson's syndrome [97,98], severe dysglycaemia [99,100], and severe arrhythmias [101,102]. They are also known to predispose to *C. difficile* infections [103].

Recent studies have shown antibiotic use in TD to increase the risk of contracting multiresistant intestinal bacteria, such as extended-spectrum beta-lactamase-producing *Enterobacteriaceae* [21–23], and called for caution in the use of antibiotics [104]. Indeed, in over 90% of cases, the symptoms of TD are only mild or moderate [2–4], and the disease resolves spontaneously. If drugs are needed by these travellers, loperamide offers a safe

alternative [27], and antibiotics are only warranted to treat severe diarrhoea. Even if their efficacy appears to increase when taken together with loperamide [43], a recent study suggests that combining the two may further increase the risk of contracting multiresistant bacteria [27]. By contrast, loperamide taken singly does not predispose to contracting MDR bacteria [27].

4.4. Decreasing efficacy of antibiotics against diarrhoeal pathogens

The potential efficacy of fluoroquinolones against TD in the tropics, especially in Southeast Asia, is severely hampered by increasing fluoroquinolone resistance among many diarrhoeal bacteria, such as *Campylobacter* [105,106,109], *Salmonella* [106,110,111], *Shigella* [106–108], ETEC [112,113] and EAEC [112,113]. Likewise, the efficacy of the alternative empiric antibiotic, azithromycin, is expected to decrease: macrolide resistance has been documented among *Campylobacter* spp. [106,109] and diarrhoeagenic *E. coli* [113], for instance. The nonabsorbable alternative, rifaximin, appears mostly ineffective against *Campylobacter* but shows good *in vitro* activity against noninvasive *Enterobacteriaceae* [106]. Besides decreased efficacy against diarrhoeal pathogens, all the three antibiotics are associated with “collateral damage” potentially leading to selecting intestinal MDR bacteria of greater public health concern [106].

5. Conclusion

The literature reviewed shows loperamide to be a safe and effective agent for TD, but only if taken according to instructions. Racecadotril, another anti-secretory drug effective against diarrhoea, has not been studied with travellers.

To our surprise, the literature search only yielded meagre data comparing loperamide alone to antibiotics; in fact, adequate proof of antibiotics being more effective than loperamide against TD was not found. Accordingly, in light of the identified drawbacks of antibiotics, it seems that they should be the drug of choice only for cases with severe diarrhoea or underlying condition that might be considerably deteriorated by TD.

In the present times, given the steadily growing antimicrobial resistance, increasing likelihood of travellers spreading the strains across the globe and importing them to their home countries, and a clear pressure to restrict the use of antibiotics during travel, loperamide may be a valuable help to travellers needing relief from the annoyance of diarrhoea while abroad.

Conflict of interest

None.

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